

Pilot Studies for Personalized Cancer Medicine: Focusing on the Patient for Treatment Selection

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Key Words. Personalized medicine • Genomics • Pilot studies • Phase I clinical trials

Learning Objectives

Describe approaches to individualized cancer treatment that are showing promise in clinical trials.

Identify barriers that exist to designing studies that provide individual, rather than aggregate, results.

ABSTRACT

Advances in diagnostics and targeted therapies during the past decade have changed how oncology is viewed. “Stratified medicine” has emerged from the accumulated evidence garnered from matching targeted therapies with tumor molecular aberrations. Concomitantly, current knowledge derived from large-scale, massively parallel sequencing technologies and global research initiatives such as the international 1000 Genomes Project, the Cancer Genome Atlas, the International Cancer Genome Consortium, and publicly available catalogs such as the Catalogue of Somatic Mutations in Cancer and Genomics of Drug Sensitivity in Cancer have illuminated the utility of understanding the molecular basis of cancer through

genome analysis. In addition, multiple collaborative efforts are widening the possibility of universally personalizing cancer care. Although several key challenges of personalized cancer medicine (PCM) need to be addressed, some pilot studies are transforming the way we analyze tumor tissue molecular aberrations, design clinical trials, and measure treatment efficacy. Taken together, these pilot studies are paving the way for clinical trials that are designed to empirically test the concept of PCM. In this paper, we describe lessons learned from the first pilot initiatives of PCM and how this knowledge is being used to design novel clinical trials. *The Oncologist* 2013;18:1180–1188

Implications for Practice: Personalized cancer medicine has changed the way oncology is envisioned. The molecular profiling of tumors seeks to take advantage of the genomic characteristics of a tumor to improve the chances of patient response to targeted agents. The analyses of genomic-driven clinical trials have shown that selecting or stratifying patients based on their molecular alterations may significantly limit the growth and spread of tumors, while sparing patients from treatment with underperforming drugs or undesirable adverse events. In this article, we discuss initiatives in personalized cancer medicine, focusing on pilot studies that have selected or stratified individual patients, moving the field closer to the practice of true personalized care.

INTRODUCTION

Historically, individual patients have helped illuminate clinical science and breakthroughs in medicine. In 1796, for example, Edward Jenner, an English country doctor, deliberately inoculated an 8-year-old boy with cowpox virus. In so doing, the physician administered a prophylactic treatment for smallpox, the world's first vaccination. Another interesting example of an individual patient contributing to clinical science is a 38-year-old male Texan who was executed but agreed to donate his body for medical research, becoming the first subject of the Visible Human Project. Similarly, in the Human Genome Project, DNA from a few donors was mixed and processed for

sequencing, including DNA from the lead scientist of Celera Genomics.

At first glance, and given the importance of informed consent in clinical research, it may appear that clinical science has continuously empowered patients at the individual level. This perception is misleading because the drug-development process currently focuses on drugs rather than patients. Several arguments support this perspective. Groups of patients are randomized either to receive or not to receive the drug being tested. Placebo is given to some individuals, who consequently derive no therapeutic benefit from participating in the

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clinical trial. In addition, some pharmaceutical companies or regulatory bodies proscribe a noncrossover policy to produce clean data for treatment approval. These policies have occasionally resulted in deleterious situations. In a clinical trial for melanoma patients that compared PLX4032, a potent inhibitor of mutated *BRAF* kinase, with dacarbazine, an underperforming older drug, two cousins were randomized and treated in different arms. The trial design prohibited crossover on progression, as requested by the U.S. Food and Drug Administration. Consequently, the two patients had significantly different outcomes [1].

Evidence-based medicine represents the optimal use of the best evidence for making decisions about patient care [2] and has become the paradigm of modern medicine; however, one could argue that such clinical research has been based on general standards of care and average populations rather than individual patients.

Personalized Cancer Medicine

Recent advances in the last decade have changed the way oncology is envisioned. Until the 1990s, treatment decisions for all cancer types were based primarily on patients' individual clinicopathological variables, disease stage, and available cytotoxic therapies. With the development of molecularly targeted agents and their widespread use, in clinical trials and the clinic, it soon became apparent that molecularly targeted agents would be more active in selected patient populations. Consequently, the drug-development process has incorporated the concept of matching therapies with biomarker-selected patient populations and integrating biomarker discovery programs into the development of novel agents. The efficacy of trastuzumab in *HER2*-amplified breast cancers [3], the PARP inhibitor olaparib in patients whose tumors harbor *BRCA1/2* mutations [4], vemurafenib for advanced *BRAF*^{V600}-mutant melanoma [5], and crizotinib in non-small cell lung cancer (NSCLC) with anaplastic lymphoma kinase (*ALK*) translocations [6] are good examples of this approach.

Given this perspective, we are witnessing a switch from histology-driven medicine to molecular clinical oncology. Because this approach to medicine is focused on selecting the optimal drug for the optimal patient, some view these examples as the birth of personalized cancer medicine (PCM) [7] (Figure 1). The current approach of matching molecularly targeted agents with single biomarkers representing specific molecular aberrations can more accurately be called "stratified medicine." The relevance of this methodology is characterized by the effect of a given drug on a molecular subgroup rather than by the effect on an individual patient. Toward this end, patients have been grouped and stratified using similar molecular characteristics, sometimes losing their uniqueness. PCM is a forward-moving approach that tailors medical treatment to the complexity of each individual patient. The aim is to concentrate the benefit of therapy for selected patients who bear or lack specific biomarkers while sparing unselected patients from treatment with underperforming drugs or undesirable adverse events.

Achievements at the individual level (e.g., initially sequenced patients in the Human Genome Project) and current knowledge derived from other collaborative efforts are widening the possibility of personalizing cancer care. These initiatives include development of large-scale, next-generation sequencing technologies and global research efforts such as

the 1000 Genomes Project [8], the Cancer Genome Atlas [9–11], the International Cancer Genome Consortium [12], publicly available catalogues such as the Catalogue of Somatic Mutations in Cancer [13] and Genomics of Drug Sensitivity in Cancer [14]. As an example, the Cancer Genome Atlas has highlighted the importance of understanding the molecular basis of cancer through multidimensional genomic analysis, including large-scale genome sequencing, analysis of DNA copy number, methylation, transcriptional profiling, and assessment of splicing aberrations [9–11].

We have also been confronted with the complexity and challenges of research in PCM, including intratumor genetic heterogeneity and clonal evolution, technical limitations of molecular tests, reimbursement and regulatory issues, the high failure rate of molecularly targeted agents, slow progress in unraveling the biology of some types of cancer [15–19], and mechanisms of resistance. The difficulty of identifying and validating predictive molecular biomarkers, signaling pathway feedback loops, molecular crosstalk, and bypass mechanisms are other examples. The performance of clinical research requires refinement to overcome these numerous challenges before personalized cancer therapies can be implemented successfully. In this paper, we discuss the current initiatives in PCM, focusing on pilot studies that address some of these challenges (Table 1). We also discuss how these pilot initiatives have focused on individual patients, moving the field closer to the practice of true PCM.

Advances in the Individualized Measurement of Treatment Efficacy

The classic Response Evaluation Criteria in Solid Tumors (RECIST) are a set of published rules that standardize radiological measurement [20]. The sum of the diameters of selected target lesions measured before treatment starts is determined and used for comparison with new radiological examinations performed at regular intervals. RECIST classifies responses into four groups based on the evolution of the size of the target lesions: complete response, partial response, stable disease, or progressive disease.

RECIST has been used in clinical research for both individual decision making and evaluation of overall treatment activity. For an individual patient, treatment is continued if there is complete or partial response or disease stability. In contrast, treatment is discontinued if disease progresses. More specifically, the overall average of lesion growth is taken into account regardless of the status of individual lesions or the growth trend of each lesion before treatment. In making drug-development decisions, individual responses are pooled and the ratio of clinical responses is compared with the response of other treatments. Consequently, the subtleties of treatment effect on individual patients and single lesions are diluted or obfuscated by aggregate data. Currently, no systematic works have addressed the limitations of RECIST throughout phase I, II, and III clinical trials; however, all of these trials might be affected because they use RECIST as a tool to assess response to treatment.

Molecularly targeted agents potentially alter the kinetics of tumor growth [21, 22], which could be missed using RECIST. Recently, the metrics of tumor-size response were evaluated so as to predict overall survival [21]. The authors

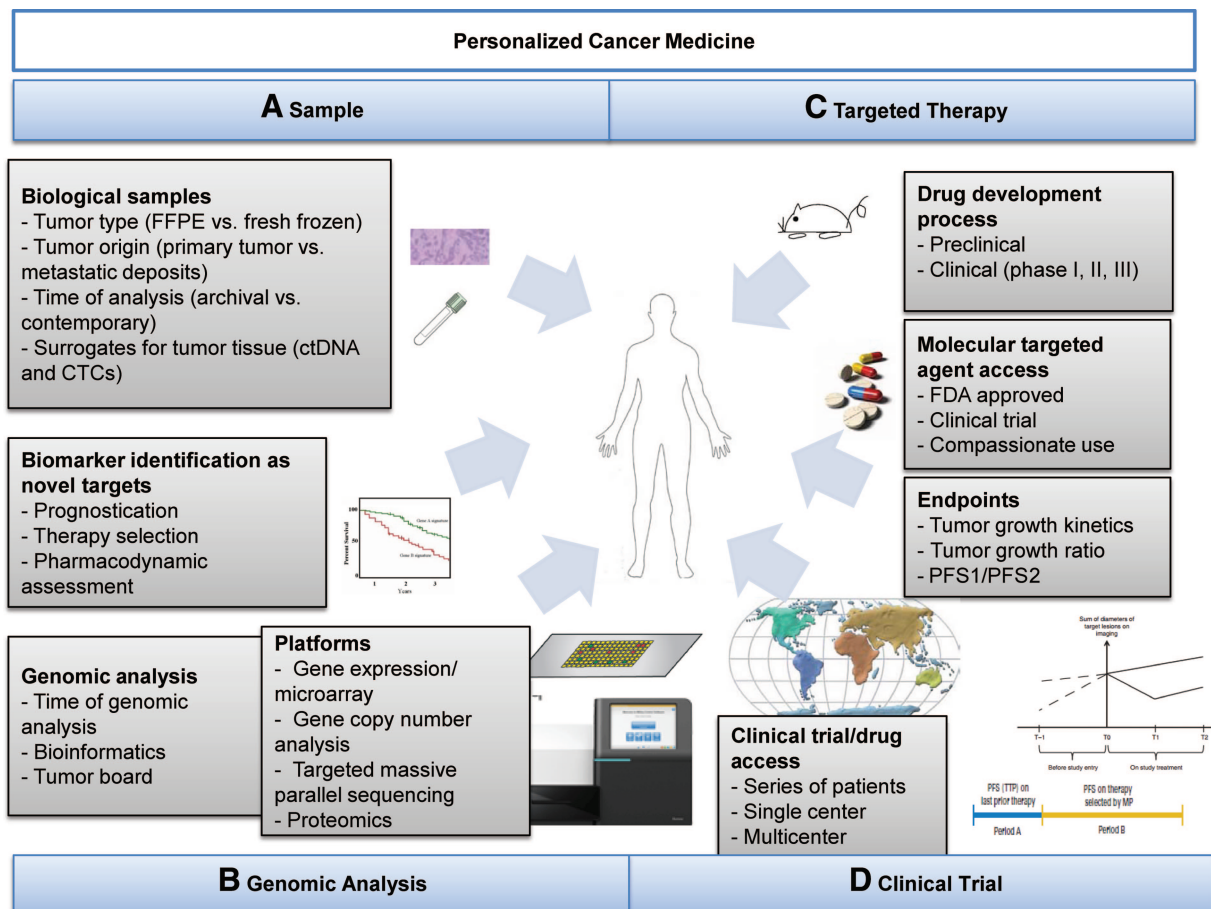


Figure 1. Personalized cancer medicine, its comprehensive nature, and its challenges presage its reality for cancer patient treatment. The figure depicts four foundations on which personalized cancer medicine relies. **(A):** Patients will have their biological samples analyzed to reveal the unique fingerprint of their genomic alterations. These biological samples include tumor tissue and/or surrogate tumor tissue markers (e.g., CTCs and ctDNA). Biomarker identification will uncover novel targets that could have a role in cancer diagnosis, prognosis, selection of an appropriate treatment plan, and monitoring of therapeutic response and resistance. **(B):** Genomic analysis has increasing importance in tailoring targeted therapy to individual patients. Apart from challenges inherent in sequencing approaches (e.g., different massively parallel sequencing platforms, huge amount of data generated, potentially actionable genomic alterations, costs of novel agents), targeting genomic alterations has the potential to improve treatment outcomes and to optimize the costs of new drug discovery in select patients while sparing others from unnecessary treatments and costs. **(C):** Matching targeted therapies with genomic molecular alterations requires a portfolio of drugs, including approved drugs, those under development, and those used as compassionate agents. **(D):** Data generated from single-center or multicenter clinical trials in oncology, particularly early clinical trials and related translational research, will likely guide further clinical drug development. New technologies for individualizing measurements of treatment efficacy are expected to help better predict responses to targeted therapies. PFS1/PFS2 indicates the ratio based on PFS endpoints using individual patients as their own controls [24].

Abbreviations: CTCs, circulating tumor cells; ctDNA, circulating tumor DNA; FDA, U.S. Food and Drug Administration; FFPE, formalin fixed and paraffin embedded; PFS, progression-free survival.

analyzed data from two phase III studies that included chemotherapy with or without added bevacizumab as first-line therapy in patients with colorectal cancer. Notably, time to tumor growth was able to capture the benefit of bevacizumab and was the best measurement to predict overall survival. When the relationship between pretreatment tumor growth rate and RECIST tumor response is compared, there can be substantial discordance [22]. In addition, the analysis of tumor growth kinetics as a continuous variable demonstrated value added to the four-category RECIST analysis in a recent study by Le Tourneau et al., which retrospectively assessed radiological data from patients treated solely with molecularly targeted agents [23]. A considerable proportion of patients without further therapeutic op-

tions discontinued therapy because of early tumor progression, based on RECIST. In contrast, tumor-growth kinetics of some of these patients who were withdrawn earlier from clinical trials were slower when compared with the beginning of treatment. This initiative represents an interesting approach to personalized therapy that standardizes the individual patient's variability of responses and uses patients as their own controls. Likewise, Von Hoff et al., investigating patients as their own controls, created a ratio based on progression-free survival (PFS) endpoints [24]. This ratio compared the PFS of patients being treated with molecularly targeted therapy with the PFS rate of the most recent therapy with which they had experienced progression. Although the results of the study by Von Hoff et al.

Table 1. Pilot studies and their potential for personalizing cancer therapy

Personalized initiative	Personalized vs. stratified	Useful for treatment decision making	Matched targeted therapy/molecular alteration	Treated patient	Used patients as their own control	Commercial agents	Clinical trials/investigational agents
Feasibility of molecular analysis for treatment decision making							
TargetNow	Personalized	Yes					
Bisgrove trial	Personalized	Yes	Yes	Yes	Yes	Yes	
MOSCATO 01	Stratified	Yes	Yes	Yes	Yes		Yes
MI-ONCOSEQ	Personalized	Yes					
COMPACT	Personalized	Yes	Yes	Yes		Yes	Yes
Bayesian statistical model							
BATTLE	Stratified	Yes	Yes	Yes		Yes	
I-SPY 2	Stratified	Yes	Yes	Yes		Yes	Yes
Matching specific targeted therapies with molecular aberrations							
The MD Anderson Cancer Center Initiative	Stratified	Yes	Yes	Yes	Yes		Yes
Patient-derived xenografts	Stratified/personalized	Yes	Yes	Yes		Yes	
Implementing personalized cancer medicine lessons in a novel trial design							
WinTHER	Personalized	Yes	Yes	Yes	Yes	Yes	Yes

Abbreviations: BATTLE, Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination; COMPACT, Canadian multicenter clinical trial; MI-ONCOSEQ, Michigan Oncology Sequencing Project; MOSCATO 01, The MOlecular Screening for CAncer Treatment and Optimisation; I-SPY 2; Investigation of Serial studies to Predict Your therapeutic response with imaging and molecular analysis; WINTHER, Worldwide Innovative Networking.

are quite appealing, they warrant further validation before widespread use.

Advances in the Individualized Analysis of Tumor Molecular Evaluation

Feasibility of Molecular Analysis for Treatment Decision Making

The Target Now program is a pilot initiative that aimed to discover targetable or actionable molecular alterations in research biopsies of patients by using immunohistochemistry, fluorescent in situ hybridization, and an oligonucleotide microarray gene expression assay in a timely fashion [25].

The Bisgrove trial aimed to use these targets for treatment decision making in a prospective multicenter pilot study that enrolled patients who were candidates for phase I trials from nine U.S. sites [24]. After a biopsy was performed and analyzed, a recommendation was given to the treating physician to use a specific regimen based on an algorithm, the presence of the target, and a broad review of the literature. A molecular target was detected for 98% of the patients. This approach resulted in superior PFS for 27% of patients who received the regimen selected through molecular profiling rather than their most recent failed therapy.

The Bisgrove trial is one of the first pilot studies using patients as their own controls to evaluate an individualized treatment decision [24]. Other insights inferred from this well-designed initiative include the ability to locate, in a timely manner, targetable biomarkers for treatment decision making (e.g., ER, HER2, EGFR, TOP2A). The study was limited by the fairly heterogeneous patient population and the use of commercially available agents only. Moreover, the relationships among the target biomarker, its predictive value, and the administered drug were questionable in many cases. The study made no mention of patient attrition, namely, the number of patients with actionable alterations who were not treated

as recommended. Importantly, actionable targets were screened for all individual patients regardless of histological and clinical characteristics. Treatment recommendations were made for all patients and led to the treatment of these individual patients as unique cases.

The Molecular Screening for Cancer Treatment Optimization (MOSCATO 01) clinical study (ClinicalTrials.gov identifier NCT01566019), using the stratified medicine approach, is an ongoing pilot initiative for enriching patients with known genomic alterations in early clinical trials. The primary goals of this initiative include the use of high-throughput molecular analysis (comparative genomic hybridization array and targeted sequencing) to select and therapeutically match metastatic cancer patients for phase I and II trials. The use of targeted therapeutics will be evaluated, and patients' PFS will be compared with their previous line of standard treatment. The secondary objectives include analysis of the clinical feasibility of such platforms and the relevance of the molecular portraits of phase I candidates.

The Michigan Oncology Sequencing Center (MI-ONCOSEQ) project is a pilot study of timely analysis with the goal of integrating massively parallel sequencing platforms with molecular-driven clinical trials [26]. Tumor biopsies from patients with metastatic cancers were systematically sequenced to translate the findings into usable tools for biomarker or mutation-driven clinical trials. In this initiative, cancer patients were recruited and provided with genetic counseling. Patient biological material was tracked from the time the tumor biopsy was performed until the results were obtained, and all genomic data were integrated (i.e., integration of whole-genome sequencing, whole-exome capture sequencing, and transcriptome analysis of tumor aberrations including structural rearrangements, copy number alteration, point mutations, and gene expression). All intermediate processes were engineered to deliver results in a reasonable time frame for making treatment decisions.

Likewise, a Canadian multicenter clinical trial, COMPACT, developed a strategy to address the systematic use of massively parallel sequencing data for PCM in a timely fashion [27]. In this multicenter clinical trial, 50 patients had tumor tissue and blood analyzed for targeted exon sequencing, multiplexed somatic mutation testing, and Sanger sequencing. The authors analyzed the possibility of incorporating real-time genomic profiling for patients with advanced cancer and created an expert panel to discuss the functional and clinical significance of molecular aberrations that were identified. Standardized reports for clinicians were also developed.

The MOSCATO 01, MI-ONCOSEQ, and COMPACT trials provided potential approaches for selecting the optimal clinical trial or approved drug for each patient. The success of these initiatives relies on the clinically relevant time frame in which actionable cancer mutations were detected. In this way, these initiatives focus on the patient. It should be noted that the MI-ONCOSEQ study, unlike the COMPACT and MOSCATO 01 trials, did not treat patients with matched therapies because no clinical trials were identified as appropriate for the patients. This brings up the caveat that in conducting such trials, ideally, a portfolio of drugs is required, including approved ones in parallel with drugs under development.

These initiatives had other drawbacks, including the need for fresh biopsies, the complexity involved in interpreting sequencing results, and the presence of incidental genomic findings. Another challenge was how to translate myriad molecular findings into selected actionable targets and recommended targeted agents. It should be noted that having actionable targets does not guarantee patient benefit from a specific targeted therapy treatment. A multidisciplinary team involving clinicians, scientists, and geneticists, together with sophisticated bioinformatics technologies, will be essential to overcome such problems. By identifying patients' genomic landscapes, these trials have generated unique databases of molecular data from metastatic disease matched with response to targeted agents.

Sampling Novelty for Personalized Initiatives

Massively Parallel Sequencing From Formalin-Fixed and Paraffin-Embedded Tumor Tissue

Presently, most available tumor samples used for molecular analysis are formalin-fixed and paraffin-embedded samples rather than freshly collected tissues. The intricate acquisition of fresh or frozen tissue samples has posed challenges for the development of platforms used to identify molecular aberrations. As an example in breast cancer, microarray-based gene expression profiling contributed toward changing our understanding of breast cancer biology over the past decade [28]; however, an obstacle to the fast clinical development of microarray-based prognostic or predictive assays in breast cancer has been the need for fresh or frozen tissue samples [29]. This may be one reason that these microarray-based platforms were not widely implemented in routine clinical practice.

Despite the increasing development of targeted therapeutic agents and massively parallel sequencing platforms, efficient and standardized methods for profiling relevant tumor genomic alterations remained to be optimized. A targeted, massively parallel sequencing approach reported by Wagle et

al. detected, with high accuracy, multiple categories of actionable genetic alterations in formalin-fixed and paraffin-embedded samples [30]. These included single-nucleotide sequence variants, small insertions and deletions, and chromosomal copy number alterations, and almost 400-fold mean sequence coverage was achieved. Initiatives such as these will facilitate the implementation of massively parallel sequencing in treatment decision making under the aegis of PCM programs.

Pilot Studies of Circulating Tumor DNA to Measure Tumor Genomic Alterations

Circulating tumor DNA (ctDNA) in plasma or serum has been widely investigated as a surrogate for tumor tissue and, consequently, has become a tool in the PCM armamentarium. The detection, quantification, and molecular characterization of plasma ctDNA has introduced new avenues for examining the metastatic process as well as new perspectives in the early detection and diagnosis of cancer [31, 32]. These biomarkers have been explored as dynamic tools for monitoring response to systemic therapies and addressing the challenges posed by therapeutic resistance and intratumor genetic heterogeneity. In this way, the sensitive "BEAMing technique" (beads, emulsification, amplification, and magnetics) has demonstrated its ability for detecting and quantifying driver somatic mutations in plasma for breast and colorectal cancers [33, 34]. As an example of the BEAMing technique, *PIK3CA* mutational status in plasma ctDNA and tumor tissues was concordant when samples were obtained simultaneously; however, when years elapsed from removal of tumor and the blood draw, discordant results were seen in as many as 20% of patients, demonstrating that biomarkers may change over time and clonal evolution may be one of the reasons.

Personalized genetic-based biomarkers using massively parallel sequencing strategies also seem to be reliable [32, 35–37]. The analysis of tumor-specific somatic rearrangements, point mutations, and copy number alterations in blood-borne specimens such as ctDNA and circulating tumor cells has demonstrated sufficient sensitivity and specificity to serve as a promising real-time liquid biopsy for cancer patients. Toward this end, more accurate decisions can be made on the basis of a longitudinal analysis of disease rather than from archival primary tumor. Moreover, ctDNA has been recently been shown to correlate with tumor burden and to provide an earlier measurement of therapy response [32]. Given the potential of genomic characterization of circulating tumor cells, ctDNA, and, recently, single cells in the context of intratumor genetic heterogeneity, these blood biomarkers are expected to be important for monitoring the emergence of treatment-resistant clones and novel ones over time and under specific selective pressures and to provide an efficient means of personalizing therapy [32, 37–40].

Advances in the Design of Trials With Individualized Selection of Therapies

Bayesian Statistical Model

The Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination, or BATTLE, trial is a biomarker-based and biopsy-mandatory prospective trial to guide treatment of heavily pretreated metastatic NSCLC patients [41]. This initiative was based on biomarker-driven subgroups and

the definition of matched therapy groups. Patients were adaptively randomized to erlotinib, vandetanib, erlotinib plus bexarotene, or sorafenib, based on relevant molecular biomarkers. The primary endpoint was achieved with 46% of 244 eligible patients exhibiting an 8-week disease control rate (DCR), mainly because of the activity of sorafenib treatment among mutant *KRAS* NSCLC patients (8-week DCR of 79%). Incorporating four different treatment arms (and pharmaceutical companies) and five different biomarker classifiers, the authors successfully integrated real-time multiplexed genotyping for identifying subgroups of patients with advanced NSCLC who were most likely to benefit from a specific agent.

This novel trial design provided important parameters. First, it focused on subgroups of patients in which multiple matches among biomarkers and molecularly driven therapies were made. Second, it used an 8-week DCR as a quickly assessable endpoint, which turned out to have a relatively low sensitivity. Finally, and perhaps most important, the design allowed a learn-as-you-go approach. The signaling pathways and targeted agents that were selected at the time the study design was devised are not currently optimal because newer findings altered the scenario of NSCLC therapy (e.g., *ALK* translocation and crizotinib approval). Despite these developments, the BATTLE trial has a relevant role within the PCM setting. It should be noted that the focus was on the molecular biomarkers rather than the individual subjects.

The BATTLE-2 Program: A Biomarker-Integrated Targeted Therapy Study (ClinicalTrials.gov identifier NCT01248247) was designed to provide individualized targeted therapy on the basis of identifying and validating specific molecular pathways underlying NSCLC. All eligible patients with advanced NSCLC will be submitted to a tumor core biopsy, and the information derived from biomarker analyses will be used to allocate patients to one of four arms of the trial: erlotinib, erlotinib plus MK-2206 (v-akt murine thymoma viral oncogene homolog [AKT] inhibitor), sorafenib, or AZD6244 (mitogen-activated protein kinase [MEK] inhibitor) plus MK-2206. This phase II trial is currently enrolling patients, and its results are eagerly awaited.

The Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis, or I-SPY 1, trial brought together a collaborative group of clinical, laboratory, and bioinformatics investigators focused on a new model for the evaluation of neoadjuvant chemotherapy in locally advanced breast cancer through the analysis of tissue biomarkers [41]. In this initiative, neoadjuvant chemotherapy was administered, and molecular biomarkers were compared with tumor response on the basis of magnetic resonance imaging findings of pathological residual disease at the time of breast surgery and 3-year disease-free survival. The trial integrated data from multiple molecular biomarker studies with imaging results and developed a robust infrastructure of optimized assays, biological material collection, tools for tissue tracking, and common information management platforms.

The I-SPY 2 initiative uses the lessons learned from the BATTLE and I-SPY 1 trials [41, 42]. The I-SPY 2 study uses an innovative adaptive trial design for high-risk breast cancer patients in the neoadjuvant setting. After an initial core biopsy, magnetic resonance imaging, and a blood sample draw, a biomarker signature will be determined. The trial will have two

arms, starting with weekly paclitaxel (plus trastuzumab in the case of HER2-positive status) followed by doxorubicin and cyclophosphamide. Initially, patients will be randomized to the novel drug agents; five new drugs will be investigated at the same time, each being added to a standard therapy. Then the adaptive design, which is based on biomarkers, will take place. Tumor tissue will be collected at surgery to assess pathological complete response, which is the primary trial endpoint. In this novel, dynamic, adaptive design, the process of learning will occur as the trial develops, and the information generated from each patient will provide subsequent treatment assignments.

Matching Specific Targeted Therapies With Molecular Aberrations

The MD Anderson Cancer Center established a program of PCM for patients undergoing phase I clinical trials (the MD Anderson Cancer Center Initiative) [43]. Tumors were analyzed for molecular aberrations, and patients received matched specific targeted therapies whenever feasible. The investigators analyzed whether identification of specific biomarkers, either genetic or molecular, along with the corresponding therapy to counteract their functional activity could improve the outcomes of patients. Many molecularly targeted agents (e.g., PI3K, MTOR, RAF, MEK, KIT, EGFR, RET, and multikinase inhibitors) and biomarkers were matched, and the results from using matched therapies were compared with the results of the previous therapy of each patient. A total of 1,144 patients were included, and 40.2% had one aberration or more. Patients with matched therapies had better outcomes than patients treated with unmatched therapies.

This initiative reinforces the need to incorporate an enriched population of patients and potential predictive biomarkers within the design of clinical trials, although the approach is more closely related to stratified medicine than to PCM. Although the observed results were positive—matched patients had higher objective responses and longer times to treatment failure—the findings should be evaluated with caution. More than half of the patients did not have any detectable molecular aberration, and many patients with molecular aberrations were not treated with a matched molecularly targeted agent. The limitations of this initiative may be partly related to the unavailability of matched drugs or the timing of therapy administration (e.g., slot availability in a phase I trial, clinical deterioration of patients). Notably, some regimens contained cytotoxic chemotherapy combined with matched molecularly targeted agents, and that might have counteracted the real effect of the targeted therapy.

Patient-Derived Xenografts

Patient-derived xenograft models reproduce the molecular characteristics of patients by engrafting tumor samples directly onto immune-compromised mice [44]. Such models have shown their utility by mimicking the effect of tumors in patients, by powerfully modeling human cancer for biomarker discovery, and potentially by guiding personalized therapeutic decisions [45–49]. In an attempt to determine novel molecular biomarkers that predict therapeutic responses, Bertolli et al. created genetically characterized xenograft cohorts from patient-derived metastatic colorectal cancer specimens [46]. *HER2* gene amplification was found in *KRAS/NRAS/BRAF/*

PIK3CA wild-type subjects, a specific subgroup resistant to cetuximab. Tumor characteristics were recapitulated, and *HER2*-amplified xenograft mice were stratified to anti-*HER2* agents with or without anti-EGFR agents. The combination of both targeted therapies produced long-term responses in some mice.

Like Bertolli et al., other studies and initiatives have shown interesting results while capitalizing on personalized platforms for making treatment decisions [50]. Research led by Hidalgo et al. produced intriguing results in terms of therapy activity and patient outcomes [48]. In a pilot trial using patient-derived xenografts for treatment decisions, patients with different types of advanced neoplasms had their therapy selected based on the agent's activity in a xenograft model, which mirrored the characteristics of their own tumors [48]. In that study, 78% of patients (11 of 14) had a partial response (i.e., 50% tumor reduction), a much higher result than the possible response achieved with conventional treatments [51]. Although a small heterogeneous population of patients was tested with commercially available agents and technical issues were present (e.g., implant failures, long time for tumor engraftment, need for large quantity of fresh tumor specimens), this achievement was remarkable for personalized therapy. Other challenges of this approach are related to tumor biology (i.e., intratumor and intertumor heterogeneity, clonal evolution) and financial issues [52]. Although the results of this pilot project seem encouraging, the logistics of translating such methods to a multicenter trial are complex.

Implementing Personalized Cancer Medicine Lessons in a Novel Trial Design: WINTHER

WINTHER is an innovative phase II clinical trial that will assess the potential of selecting targeting therapies according to the tumor biology of patients [53, 54]. It was launched by the Worldwide Innovative Networking Consortium, also called the WIN Consortium, in PCM. The trial design and methods incorporated many of the lessons learned from the prior experiences described in this article.

The trial will explore a rational choice of therapeutics and their efficacy beyond current limitations. From each patient's biopsy of the tumor (or metastasis) and normal tissue, a complete biological analysis of DNA, RNA, and microRNA will be undertaken. The choice of therapy will be rationally guided either by matching actionable targets found in the tumor analysis (matching drug and molecular alterations, arm A) or tumor gene expression and predicted sensitivity of the drug (matching differentially expressed genes between tumor and normal tissue with drugs, arm B). The efficacy assessment is also individually evaluated because it is based on the time frame that patients are on the former therapy (period A) compared with the time frame of the WINTHER therapy (period B). If period B is greater than period A, the gene profiling-selected therapy will be identified as having changed the natural history of the patient's disease.

In the WINTHER initiative, the feasibility of collecting and analyzing tissue in a multicenter fashion will be tested and has the purpose of constructing a workflow for clinical decision making using massively parallel sequencing and/or microarray platforms. An algorithm for predicting drug sensitivity based on differential gene expression between tumor and

normal tissue will also be evaluated. This trial represents a comprehensive, tailored enterprise in which tumor and normal tissue from patients will be analyzed and compared and in which patients act as their own controls for evaluating treatment efficacy.

CONCLUSION

Individual tumors are composed of a variety of molecular alterations that can be informative and potentially targetable through treatment decision making. PCM initiatives have taken advantage of these aberrations to focus on single individuals and their molecular identities, with the ultimate aim of tailoring therapy to produce beneficial clinical outcomes and to overcome therapeutic resistance. Most of these initiatives have focused on individual patients by identifying groups of patients who share similar targetable biomarkers and tailoring appropriate potential targeted therapies to them. In contrast, a few other initiatives have given priority to the stratification approach, with a focus on molecular biomarkers rather than individual patients.

Various challenges will have to be addressed to successfully implement the insights already derived from these PCM pilot studies. Access to oncological therapies can be problematic because it depends on the availability of clinical trials and issues related to those trials in terms of adequate inclusion criteria, availability of slots to treat patients in a timely manner, and selection of appropriate drugs and therapeutic dose levels. Access to the compassionate use of specific agents and the use of drugs outside their regulatory agency-approved indication are other challenges. Because the number of genetic biomarkers known to influence patient outcomes and care has risen considerably in recent years and massively parallel sequencing has become more available, some oncologists are already taking advantage of these tools in day-to-day practical medicine; however, drawbacks remain in the assessment of targeted therapy outside of clinical trials or by compassionate use and the fact that these approaches are not yet evidence based. Combinations of drugs, be they cytotoxic chemotherapy combined with targeted agents or combinations of two or more targeted agents with complementary mechanisms of action, are expected to provide the means to counteract the almost universal occurrence of therapeutic resistance associated with cancer treatment. The role of each drug would be best understood if independently evaluated for target effectiveness. In addition, N-of-1 clinical trial designs or single-subject clinical trials, which explore an individual patient for efficacy or side-effect profiles of different interventions, have become increasingly relevant to investigate the value of individualized therapy, particularly for patients that harbor rare molecular aberrations.

Another challenge is that the interpretation of molecular analyses through the increasing use of massively parallel sequencing platforms is complex, and this has hampered direct application of known molecular aberrations in the clinic to targeted agents. Genetic heterogeneity at intratumoral and interpatient levels and clonal evolution of tumors over time are among the present challenges. This is especially true considering the common practice of relying on a single biopsy, which cannot reflect the frequently heterogeneous molecular landscape of tumors and frequently leads to sample bias. It is

hoped that, in the near future, novel molecular tools including surrogate tissue markers (i.e., circulating biomarkers and molecular imaging) will be standardized and validated to provide the ability to overcome the drawbacks associated with tumor tissue alone. Importantly, functional characterization of tumor-derived biomarkers and patient-derived xenografts represents another important emerging area because these tools may provide tangible evidence of the benefit of rationally guiding personalized approaches.

Finally, reimbursement policies and costs inherent to all these efforts that include molecular analyses, drug administration, the cost of drugs, patient care, and bureaucratic issues should be globally analyzed to ensure that academia and industry provide well-defined input.

Although some individual patients have made outstanding contributions to medicine, PCM has had increasing importance in defining the most appropriate drug for each patient. The clinical utility of personalized medicine has not been established, yet some patients with molecular aberrations matched with specific molecularly targeted agents have benefited from transient in-

creases in their time to disease progression, and medical oncology practitioners have taken advantage of these personalized approaches. Many difficulties are likely to be overcome in the next few years, and the first steps toward a universal setting of PCM focused on patients for treatment selection are already making significant progress.

AUTHOR CONTRIBUTIONS

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Collection and/or assembly of data: Jordi Rodon, Leticia De Mattos-Arruda

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